## REMARKS

Reconsideration of the application is respectfully requested. Claims 21, 25, 27, 31, 33, and 37 are pending and at issue.

## Obviousness Rejection

Claims 21, 23, 25, 27, 29, 31, 33, 35, and 37 have been rejected under 35 U.S.C. § 103(a) as obvious over Patris et al. (*Int. Clin. Psychopharm.* 11:129-136 (1996)) in view of Boegesoe et al. (U.S. Patent No. 4,943,590), and Bilski et al. (U.S. Patent No. 4,764,361). The Examiner cites Patris as disclosing administration of citalopram to treat patients with major depression, with efficacy measured using MADRS scores and the CGI severity and improvement scale. The Examiner concedes that Patris does not teach escitalopram. The Examiner cites Boegesoe as disclosing that the entire 5-HT uptake inhibition activity in racemic citalopram resides in escitalopram. The Examiner cites Bilski as generally teaching the oxalate and crystalline salts of the (S) form of a racemic mixture, but acknowledges that Bilski does not disclose escitalopram. From the foregoing, the Examiner concludes that it would have been obvious to use the crystalline and oxalate salts of escitalopram to treat severe depression.

Claims 23, 29, and 35 were canceled in the Response file September 27, 2007. Therefore, the rejection of these claims is moot. As to the remaining claims, this rejection is traversed and reconsideration is respectfully requested.

Claims 21, 25, 27, 31, 33, and 37 are not obvious because, *inter alia*, there are unexpected results associated with the claimed methods, which are significant and rebut the Examiner's obviousness rejection.

An applicant can rebut a presumption of obviousness by showing "that there are new and unexpected results relative to the prior art." MPEP §2144.05 (quoting *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)). The Examiner contends, however, that Applicants' "disclosure of several published articles supporting the surprising

effect of treating severely depressed patients with escitalopram is of no consequence in the absence of any substantial disclosure in the instant specification elucidating such findings." Office Action, p. 4. To support this position, the Examiner relies on Svensson, et al., *Psychother Psychosom.* 73(1):10-6 (Jan-Feb 2004) (Abstract), which refers to a study designed to assess whether there is justification for advertising claims made by the manufacturer of escitalopram regarding the drug's efficacy and speed of onset.

The Svensson abstract relates solely to *advertising claims* and not to whether escitalopram provides unexpectedly superior efficacy compared to citalopram in the treatment of severe depression. Svensson was published in 2004 and thus pre-dates several studies demonstrating the therapeutic superiority of escitalopram over citalopram in treating severe depression. *See, e.g.*, Lam, et al. *Pharmacopsychiatry*, 39:180-84 (2006); Moore et al., *Int. Clin. Psychopharm.*, 20(3):131-37 (2005); Yevtushenko et al., *Clinical Therapeutics*, 29(11):1-14 (2007) (copies of Lam and Moore were submitted with the September 27, 2007 Response; a copy of Yevtushenko is submitted herewith as Attachment A). Hence, later-published evidence clearly shows that escitalopram is superior to citalopram. Had Svensson considered these studies in its survey of drug trials, it may have concluded that the price of escitalopram is indeed justified.

Importantly, the Svensson abstract focuses specifically on this issue of commercial pricing - i.e., whether certain advertising claims "justify higher prices" (*see* Abstract). Whether or not advertising claims justify certain market prices is not relevant to a determination of obviousness under 35 U.S.C. § 103(a).

What is relevant is evidence of unexpected results. It is well established that "[a] greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, (Fed. Cir. 1985); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007) ("Evidence of unexpected results can be used to rebut a prima facie case of obviousness."). Additionally, it must be shown that the results were greater than those that would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. *In re Glaug*, 283

F.3d 1335, 1341 (Fed. Cir. 2002); *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991).

Here, the Examiner has acknowledged Applicants' previously submitted evidence as "supporting the surprising effect of treating severely depressed patients with escitalopram." Office Action, p. 4. In particular, this evidence includes several studies showing that escitalopram has unexpectedly superior efficacy compared to citalopram in patients suffering from severe depression and having a MADRS score of at least 29. *See, e.g.*, Gorman et al., *MedWorks Media*, April 2002; Lam, et al. *Pharmacopsychiatry*, 39:180-84 (2006); Lepola et al., *Int. Clin. Psychopharmacol.*; 19:149-55 (2004); Moore et al., *Int. Clin. Psychopharm.*, 20(3):131-37 (2005) (copies submitted with the September 27, 2007 Response). Each of these studies report a "greater than expected result" providing a clinically "practical advantage."

Even more evidence of this "greater than expected result" is found in a 2007 study of the comparative efficacy and tolerability of 10-mg/day escitalopram and 10- and 20-mg/day citalopram in patients with major depressive disorder (MDD). *See* Yevtushenko et al., *Clinical Therapeutics*, 29(11):1-14 (2007) (Attachment A). The Yevtushenko study involved the treatment of 322 MDD patients having a MADRS score of 25 or greater, including a subgroup of severely depressed patients having a baseline MADRS score of 35 or greater (Abstract; p. 4). The authors found (p. 5; p. 8 (Table II)):

> In the severely depressed subpopulation, the differences in mean (SE) change from baseline to end point in MADRS score between the escitalopram group (n=66) and the citalopram 10- and 20-mg groups (n=65 and 78, respectively) were ... significant beginning at week 1.

In fact, the patients in the severely depressed subgroup showed the most improvement in this study. Specifically, the authors found that "the difference in the MADRS score at study end was >3.5, suggesting that the difference on MADRS between escitalopram and citalopram is clinically relevant, with the largest difference evident in the severely depressed subgroup (MADRS score, ≥35)" (p. 11). This is especially notable because "[s]ome authors have suggested previously that a 2-point difference in the MADRS score should be considered

clinically meaningful" (p. 11). The authors further concluded that these results were "consistent with those from previously published studies," such as Moore et al., *Int. Clin. Psychopharm.*, 20(3):131-137 (2005) (copy submitted with the September 27, 2007 Response). *See* p. 11 (left col.) of Yevtushenko. In summary, the Yevtushenko study confirms that escitalopram (the S-enantiomer) has unexpectedly superior efficacy compared to citalopram (the racemate) in patients suffering from severe depression and having a MADRS score of at least 29.

The specification also provides several examples of "greater than expected" results. For instance, the specification discloses that administration of citalopram surprisingly did not lower patients' MADRS scores as much as administration of escitalopram, and highlights the inventors' surprising discovery that the R-enantiomer in citalopram has a *negative* effect on escitalopram, resulting in citalopram's inferior efficacy in severely depressed patients. *See* Specification, p. 2, lines 13-14. The foregoing evidence is sufficient to rebut the Examiner's obviousness rejection and no additional arguments or evidence justifying the commercial pricing scheme of escitalopram is either necessary or relevant.

The Examiner also contends that: (i) the specification lacks a "quality assessment instrument;" (ii) the specification lacks data regarding the MADRS factors or how this scale is incorporated into the claimed invention; and (iii) a skilled artisan would "not be inclined" to correlate the disclosure in the specification with unexpected results, such as those found in the supporting articles previously submitted in connection with this application (*see* Gorman (2002); Lam (2006); Lepola (2004); Moore (2005)).

Regarding the "quality assessment instrument," U.S. patent law does not require a specification that discloses experimental data to also disclose an instrument for evaluating the "quality" of that data. Nevertheless, the present specification does, in fact, provide a quality assessment instrument in the form of "p" values for its clinical results. *See* Specification, p. 6, line 19 to p. 7, line 9. P values are well accepted in the field as indicators of statistical significance.

Regarding MADRS data and its relevance to the instant invention, Applicants note that the MADRS scale has been used since 1979 to measure the severity of depressive episodes in patients with mood disorders, and is commonly accepted by those skilled in the art as a reliable diagnostic indicator of the severity of a patient's depression. Because the MADRS scale is well known and accepted in the art, it need not be disclosed in detail. *See Falkner*, 448 F.3d 1357, 1365 (Fed. Cir. 2006) ("[A] patent need not teach, and preferably omits, what is well known in the art.") (quoting *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed. Cir. 1987)). Further, there is no requirement that applicants disclose tomes of raw data underlying experimental results provided in a specification. Here, the instant specification discloses a study of 468 patients over an 8-week period, which demonstrated the unexpected superiority of escitalopram. This corresponds to a large quantity of data, including that collected using the MADRS scale. The purpose of such diagnostic scales is to provide skilled artisans with meaningful assessments based on multiple factors - not to collect and present reams of individual data. Only when considered as a whole can it be determined if the data are statistically significant. Such a determination is expressly disclosed in the present specification. *See* Specification, p. 6, line 31 to p. 7, line 3.

Regarding one of ordinary skill being "inclined" to correlate the disclosure in the specification with unexpected results, it is again asserted that no such requirement exists under U.S. patent law. That is, the specification need not "incline" a skilled artisan to identify a correlation. Nevertheless, the correlation is explicitly stated in the present specification, which discloses that escitalopram is superior to citalopram in treating severe depression. *See* Specification, p. 7, lines 5-9. The results from the clinical study disclosed in the specification readily show this correlation.

The Examiner states that Bilski teaches "the oxalate and crystalline oxalate salts of the (S) [sic] are a form of a racemic mixture." *See* page 6 of the Office Action. Contrary to the Examiner's statement, Bilski does not teach the oxalate and crystalline salts of the (S) form of a compound in a racemic mixture. Rather Bilski teaches the oxalate salt of the (S)-enantiomer of one specific compound. A crystalline citalopram salt does not contain crystalline escitalopram

(S-citalopram). Citalopram crystallizes as a racemate, i.e., the unit cell of the crystal contains both enantiomers in equal proportions. In contrast, the unit cell of an escitalopram crystal only contains the S-enantiomer.

For the foregoing reasons, the presently claimed invention is not obvious over the cited references. Applicants, therefore, respectfully request that this rejection be withdrawn.

**Conclusion**

In view of these remarks and arguments, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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